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Utilization of health care services by patients with chronic obstructive pulmonary disease

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Abstract In order to identify healthcare resource use patterns associated with chronic obstructive pulmonary disease (COPD), resource utilization (RU) data collection was integrated into a randomized, double-blind placebo-controlled study of Viozan™ (sibenadet HCl). This study enrolled patients with symptomatic, smoking-related COPD, randomized to receive sibenadet or placebo for a 52-week treatment period. A questionnaire establishing typical pre-trial, COPD-related RU was completed by each patient. Subsequent data were collected by means of an Interactive Voice Response System (IVRS) at 30-day intervals (14 time points) during the study and in the follow-up period. The IVRS system facilitated data collection and minimized inconvenience to the patient. Compliance with the requirement to record details of the healthcare services during the year-long study was high.

No overall trend for lower RU was associated with sibenadet therapy, which correlates with the lack of sustained clinical effect seen in studies conducted concurrently. These data do, however, provide valuable information on RU associated with COPD and insights into adjustments associated with changes in disease course. Physicians were seen to be the most common source of care for patients with COPD and more of the patients with severe COPD (stage III) than mild (stage I) were seen to utilize the most expensive resources (e.g. inpatient hospital care). For those patients who experienced an exacerbation during the trial (irrespective of treatment group), resource use was increased during the periods when an exacerbation was reported when compared with the periods before or after an exacerbation. The proportion of cases attending the physician doubled and with a trip to the Emergency Room (ER) increased approximately ninefold during the reporting period in which the exacerbation occurred compared with the previous month.

This study has shown that use of an IVRS, even in elderly patients, is an effective means of gathering RU data over long periods. The study findings suggest that the advent of effective therapeutic interventions, particularly any with the ability to minimize exacerbations and limit disease progression, could impact on the health care services used and potentially reduce associated costs.

Keywords chronic obstructive pulmonary disease (COPD); resource utilization; exacerbations; sibenadet HCl; disease severity.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide; it is believed that around 16 million people suffer from COPD in the U.S.A. alone (1). As many patients remain undiagnosed, an accurate determination of global prevalence is extremely difficult but has been estimated to be around 4–6% in those over the age of 45 years (2). COPD is a leading cause of death, predicted to increase in prevalence worldwide (3).

COPD occurs primarily in elderly, long-term smokers and is characterized by the key symptoms of breathlessness, cough and sputum (4–5). The disease course of COPD is extremely slow, meaning that patients will suffer the symptoms of disease for many years or even decades. The associated economic impact is considerable although limited pharmaco-economic analyses have been performed and detailed information is available only from North America and some European countries (6). Published U.S data reported in 1993 estimated the total cost related to COPD management to be $23·9 billion. Direct medical costs accounted for 62% of the total, with

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hospitalizations accounting for a substantial proportion of the direct medical cost (6). It is estimated that the direct costs of COPD are twice those of asthma (6).

In contrast to other chronic conditions, the proportion of healthcare costs attributed to medication is relatively low for patients with COPD (7), the greatest proportion of direct costs associated with COPD being long-term oxygen therapy and hospitalization (7–9).

A strong correlation between stage of disease and treatment costs has been demonstrated, with increased utilization of clinic, emergency department and hospital visits associated with a more advanced stage of disease (10). A proportion of these increased costs will be due to an increased frequency of exacerbations necessitating emergency visits or hospitalization amongst patients at a more severe stage of COPD (11). Previous studies in the U.S.A. have shown healthcare utilization among patients with COPD to be disproportionately distributed, with a small proportion of the patients (approximately 10%) accounting for at least half of the expenditure, with hospitalization being an important component of that expense (12–13). Supplemental home oxygen constitutes a large proportion of outpatient costs (7). The need for long-term treatment means that oxygen therapy, along with hospitalization, nursing home care, physician visits and medication are the major cost drivers in COPD (7). As requirement for these interventions increases with disease severity, disease stage can be considered to be a key factor in resource utilization (RU).

Patients participating in a 1-year safety study of the novel D_2 dopamine receptor, β_2-adrenoceptor agonist, Viozan™ (sibenadet HCl) were recruited to participate in a parallel RU study, the results of which are reported here. The objectives of this secondary investigation were twofold; first to identify overall RU in patients with symptomatic, smoking-related COPD and second to discern any differential RU associated with different treatment strategies.

METHODS

RU data were collected from patients participating in a long-term placebo-controlled safety study of sibenadet, the details of which are reported by Hiller *et al.* (14). The RU data collection process was designed to provide the means to collect not only overall COPD management-related RU patterns, but also health care service use by treatment arm.

Clinical trial design

Patient population

The safety study recruited male and female patients (aged 40–80 years) with stable, uncomplicated COPD (with symptoms for at least 2 years). Subjects were required to be current or ex smokers with a smoking history of at least 15 pack-years (where 1 pack year = 20 cigarettes smoked per day for 1 year or equivalent). Additional inclusion criteria were a forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio of ≤ 70%, and an FEV_1 20–70% of predicted normal range.

Patients not eligible for the study included those with other significant diseases, evidence of a COPD exacerbation in the previous 6 weeks, previous participation in a clinical study of sibenadet, participation in any clinical study in the previous 3 months, laboratory abnormalities or use of disallowed medication. Patients were allowed to continue using inhaled anticholinergic agents, mucolytics, methylxanthines and corticosteroids, provided that the dose remained constant throughout the study.

Study design

RU data were collected from patients randomized to a double-blind, placebo-controlled study of sibenadet (14). The RU data were collected from patients recruited at 43 centres in the U.S.A. Eligible patients were enrolled and entered a 2-week baseline assessment period. Disallowed medication was withdrawn and salbutamol inhalers were supplied for use as rescue medication when required. At the end of the baseline period, patients who had completed their diary card correctly and had not experienced COPD exacerbations were randomized to receive either 500 μg (ex-actuator) sibenadet or placebo pressurized metered-dose inhaler (pMDI) three times daily for a total of 52 weeks. At the end of the treatment period, sibenadet and placebo inhalers were withdrawn, and patients were required to continue using only rescue medication during a 4-week follow-up period until the final clinic visit. Diary cards were completed by patients throughout the study to record use of study and rescue medication, changes in concomitant medication, and adverse events.

The study was performed in accordance with the principles stated in the Declaration of Helsinki and approved by ethics committees at each centre. To ensure confidentiality throughout collection of RU data, patients were referred to by a patient identification number only.

Collection of healthcare RU data

The primary objective for collecting RU data as part of the clinical study was to identify RU patterns in COPD by treatment arm in order to determine if any differential use profiles existed.

Data collection procedure

COPD-related healthcare RU data were collected on all patients randomized to treatment. At the end of the

baseline period, RU questionnaires were completed by the patients to record COPD-related medical care received in a typical month and health care service use (e.g. hospitalization, emergency room (ER) visit) in the 3 months prior to the start of the clinical trial. The questionnaire recorded demographic information (gender, age, functional independence level, and regular oxygen use). The following healthcare services were summarized: physician, nurse, therapists (i.e. physical, occupational, respiratory), psychotherapist, or social worker visits; paid domestic help; COPD-related ER visits and acute hospital stays.

RU data were subsequently collected at 30-day intervals (14 in total) during the treatment and follow-up periods of the trial. Patients were asked to report, by telephone, healthcare services used for the previous 30-day reporting period. A healthcare resource use tracking aid and written instructions were provided to facilitate recall. The interactive voice response system (IVRS) was utilized by all patients with a touch-tone phone (97%). The remaining 3% of study patients reported their data via a telephone interview.

RU data collection was designed and managed by Caro Research (Concord, MA, U.S.A.) who also conducted all RU-related analyses.

Data from the clinical trial allowed further analyses by disease severity, disease duration and clinical exacerbations. COPD severity was noted as stage I (FEV_1 % predicted ≥ 50), II (FEV_1 % predicted 35–49) or III (FEV_1 % predicted < 35) as defined by the American Thoracic Society (4). Clinical exacerbations were defined as worsening symptoms of COPD requiring drug therapy in addition to study medication (study drug and rescue medication) and doses of concomitant COPD medications. In addition, any adverse event description that contained both the words 'COPD' and 'exacerbation' was also considered to be a relevant COPD exacerbation.

Analyses

The baseline characteristics are reported by gender, age (< 65/≥ 65 years), current smoking status, stage and duration of COPD. The proportions of patients using each service during a typical month before the trial and during the trial were determined and compared between treatment groups. For users of a service, the mean use per month was determined. In addition, analyses were undertaken for the subgroup of patients experiencing exacerbations.

Initial analyses employed the intention to treat (ITT) principle with all data from the RU population included in all analyses irrespective of compliance with study medications or protocol deviations.

RU was compared before, during and after a period when a clinical exacerbation of the disease was recorded. This required identification of the subgroup of the patients providing RU data that experienced an exacerbation (i.e. patients without an exacerbation are excluded) with RU data reported in the period before or after the exacerbation (i.e. some exacerbations were excluded).

Table 1. Baseline patient characteristics

Characteristic	Trial RU data reported (*n*=393)
Gender	
Male	228 (58·0%)
Female	165 (42·0%)
Age	
< 65 years	176 (44·8%)
≥ 65 years	217 (55·2%)
Smoking status	
Current smoker	159 (40·5%)
Previous smoker	234 (59·5%)
COPD stage	
Stage I	108 (27·5%)
Stage II	144 (36·6%)
Stage III	141 (35·9%)
Duration of COPD	
≤ 3 years	125 (31·8%)
4–5 years	89 (22·7%)
6–9 years	92 (23·4%)
≥ 10 years	87 (22·1%)

RESULTS

Patient characteristics

A total of 434 patients completed the pre-trial RU questionnaire; 41 patients dropped out of the trial before reporting any RU information by telephone. All 393 remaining patients reported RU data at least once during the trial. Compliance with providing details of RU during the course of the study was high. Of those who started the trial, 64·2% reported data for 12 or more periods. Data were reported for all 14 periods by 137 subjects (34·9%). Of the 72% who completed the trial and reported RU data, 89% provided data for 12 or more periods. Baseline demographic data (Table 1) showed that the majority of patients reporting RU data were male, over 65 years of age and had been diagnosed with COPD within the last 5 years.

Resource utilization results

RU recorded at baseline (obtained from 434 patients completing the pretrial RU assessment questionnaire) indicated that before starting the trial the most frequently used services were medical doctor visits, which were reported by 16·2% of patients during the

Table 2. RU during the trial

Resource	Proportion of patients using the service during the trial (n=393)	Mean (SD) per month by users of the service
Physician visit	72·5%	1·8 (1·2)
Oxygen use at home (at least once per week)	19·6%	N/A
Respiratory therapist visit	17·1%	11·1 (16·4)
Nurse visit	10·7%	3·2 (4·0)
Other health care professional visit*	< 6·6%	N/A
Emergency Room visit	13·5%	1·3 (0·6)
Hospital admission	16·3%	Mean length of stay 2·0 days (2·1)

*Social worker, physical or occupational therapist or psychotherapist

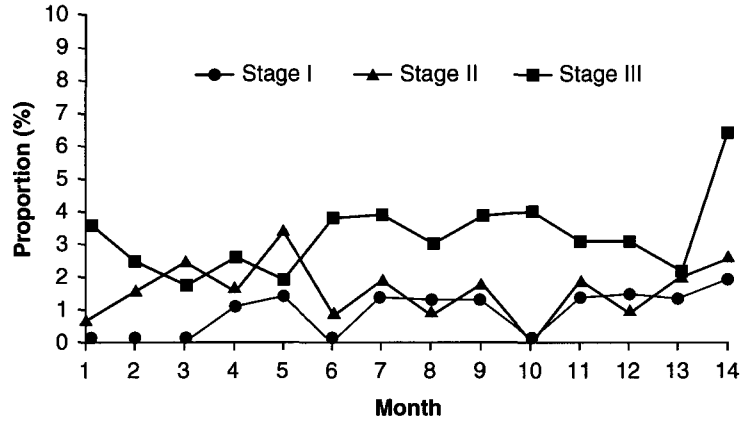

FIGURE 1. Proportion of patients reporting hospitalization in each data reporting period by COPD severity.

past month, and approximately 13·6% used oxygen at least once each week. There were no differences in the pretrial RU profiles of the treatment groups, except that significantly more of the placebo group had typically visited a respiratory therapist.

Resource use during the study period was obtained from 393 patients. Of the ITT population, 79% reported use of one of the resources at least once during the trial period. Physician visits were the most common resource used, with 72·5% reporting at least one visit (Table 2). Less than 5% of the patients visited each of the other health care professionals in each 30-day data-reporting period. Few patients visited a physical therapist (6·6%) once during the trial and < 2·3% received care at least once from a social worker, occupational therapist, or psychotherapist. During the course of the trial, a small group of patients were not able to receive all their medical care in an outpatient setting – 16·3% were admitted to hospital and 13·5% attended an emergency room. Paid housekeeping or domestic help services were used at least once during the trial by 7·9% of the patients, for an average of 12·2 hours per month.

Few differences in RU were seen between patients randomized to placebo or sibenadet therapy. Differences were, however, seen in terms of physician and ER visits. Patients receiving sibenadet reported a lower rate of physician visits (68·4% *vs.* 80·8% for placebo, P=0·010) and a lower rate of ER visits than those receiving placebo (11·0% *vs.* 18·5%, P=0·042).

Resource use and disease stage

Patients with more severe disease (Stage III) were more than twice as likely to be using oxygen at least once during the trial as those at Stage I or II (30% *vs.* 13·9% for Stage I and 13·2% for Stage II, $P < 0·001$). More severe disease was also associated with an increased risk of an ER visit or hospitalization during the trial. Patients at Stage III were more likely to report hospitalization (25·5% *vs.* 7·4% for Stage I and 13·9% for Stage II, $P < 0·001$) (Figure 1) or an ER visit and hospitalization (15·6% *vs.* 2·8% for Stage I and 6·9% for Stage II, P=0·001) during the same period.

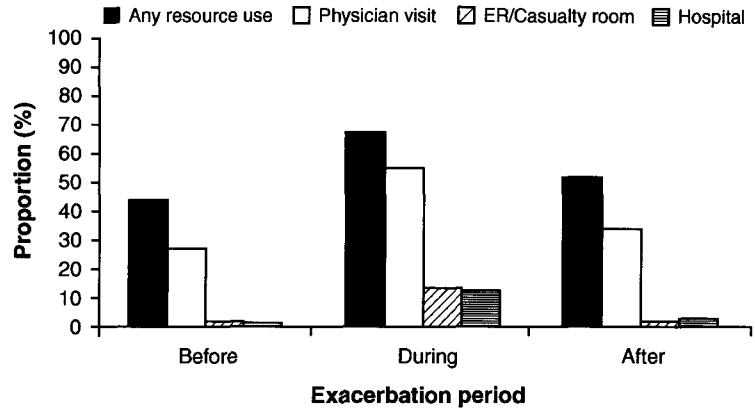

FIGURE 2. Proportion of cases reporting any COPD-related healthcare RU – before, during and after periods of exacerbation.

Exacerbations and resource use

From a subset of 184 patients who experienced an exacerbation during the trial period and provided RU data, information from 372 exacerbations were collected across both treatment groups. From these, data were collected from a period preceding the exacerbation in 198 cases, during an exacerbation for 241 cases and after an exacerbation for 204 cases. Resource use was increased during the periods when an exacerbation was reported compared with the periods before or after an exacerbation (Figure 2). The proportion reporting use of any healthcare service increased from 43·9% of subjects in the period preceding, to 67·6% during the exacerbation ($P < 0{\cdot}0001$). This increase was sustained post-exacerbation, when 52% of cases used at least one service. Physician visits increased from 27·3% to 55·2%, ER visits from 1·5% to 13·7% and hospitalizations from 1·0% to 13·3%.

DISCUSSION

The primary objective of this study was to identify RU patterns by treatment arm in patients with COPD in order to determine if a differential cost profile could be established in a later analysis. Sibenadet therapy, however, failed to demonstrate significant efficacy benefits in any of the large-scale clinical studies conducted (14–16). The data collected during this study provide interesting additional information on RU associated with COPD and insights into adjustments associated with changes in disease course. Being part of a clinical study, the RU information obtained represents a well-defined patient group assessed under highly controlled conditions. While this situation is desirable for data collection, participation in a trial may also have influenced the RU profiles, partly due to the scheduled visits during the trial, and also due to the fact that patients were required to meet very specific inclusion and exclusion criteria for entry into the study. The RU profiles detailed here are, therefore, representative of the services used by this trial population, and may not be typical of the services used by all patients diagnosed with COPD. For example, patients with COPD commonly have comorbidities such as congestive heart failure, and this has been shown to substantially influence health care service utilization and costs (12).

Compliance with reporting RU data was good; almost two-thirds of the patients reported 12 or more periods worth of data and over a third of the patients provided all reports. Supplying a carefully designed tracking aid facilitated recall of the services used during the period and continued participation was encouraged by the convenience of using the IVRS. Although patient discontinuation from the clinical study of almost one third (14) may have introduced some bias into the RU estimates, compliance with reporting requirements will have limited the impact of drop-outs.

Analysis of healthcare utilization confirmed that physicians are the most common source of care for patients with COPD; about one-third of the patients reported a physician visit in each 30-day reporting period. Additional RU was, however, generally low although our findings indicate that a small group of patients required inpatient care. This is consistent with other studies that found a small proportion of patients (approximately 10%) account for at least half the expenditure, hospitalization being an important component of that expenditure (6,12). As reported in previous studies (10) stage of disease was seen to be an important factor influencing use of services. Home oxygen therapy and hospitalization account for a substantial proportion of expenditure when caring for patients with COPD (7). This RU assessment has shown that three times as many patients at a more severe stage of disease (Stage III) compared with mild disease (Stage I) were hospitalized at least once during the study. As previously noted, oxygen use also increased with disease severity (10).

Patients with COPD experience exacerbations of their disease, which may be associated with bacterial or viral infections (4). Substantially higher RU was observed for all services (with the exception of oxygen use) during the period when an exacerbation was reported compared to before or after the exacerbation. During the period of an exacerbation the proportion reporting a physician visit was approximately twice that reported in the period prior to an exacerbation. In addition, approximately 13·7% reported an ER visit or hospitalization during an exacerbation period, at least a ninefold increase from the previous period. Exacerbations are therefore clearly associated with increased use of inpatient and outpatient services. Information on concomitant medication was not collected as part of this resource use study, but may have provided further insights into the exacerbation scenario.

Although no cost analyses were performed as part of this study, it is possible to consider that effective therapy may have the potential to generate savings to justify the cost of a new treatment. In particular, treatment that can effectively reduce the rate and severity of exacerbations is likely to reduce inpatient RU and increase use of less costly outpatient care. Such analyses should therefore form an important aspect of the overall assessment of future novel therapies, although longer-term studies that describe associated costs and the use of cost-effectiveness analyses will be required to adequately describe the cost implications of RU to payers.

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REFERENCES

1. Adams PF, Hendershot GE, Marano MA. Current estimates from the National Health Interview Survey 1996. National Center for Health Statistics. *Vital Health Stat* 1999; **10:** 200.
2. O'Byrne PM, Postma DS. The many faces of airway inflammation, asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; **159**: S41–S66.
3. Murray JL, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global burden of disease study. *Lancet* 1997; **349:** 1498–1504.
4. American Thoracic Society. Standards for the diagnosis and care of patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 1995; **152**: S77–S120.
5. Pauwels RA, Buist AS, Calverley PM, *et al.* Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: National Heart, Lung and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. *Am J Respir Crit Care Med* 2001; **163:** 1256–1276.
6. Sullivan SD, Ramsey SD, Lee TA. The economic burden of COPD. *Chest* 2000; **117**: 5S–9S.
7. Ward MM, Javitz HS, Smith WM, Bakst A. Direct medical cost of chronic obstructive pulmonary disease in the USA. *Respir Med* 2000; **94**: 1123–1129.
8. Strassels SA, Smith DH, Sullivan SD, Mahajan PS. The costs of treating COPD in the United States. *Chest* 2001; **119**: 344–352.
9. Rutten van-Mölken MPMH, Feenstra TL. The burden of asthma and chronic obstructive pulmonary disease. *Pharmacoeconomics* 2001; **19** (Suppl 2): 1–6.
10. Hilleman DE, Dewan N, Malesker M, Friedman M. Pharmacoeconomic evaluation of COPD. *Chest* 2000; **118**: 1278–1285.
11. Andersson F, Borg S, Jansson S-A, *et al.* The costs of exacerbations in chronic obstructive pulmonary disease (COPD). *Respir Med* 2003: in press.
12. Grasso ME, Weller WE, Shaffer TJ, *et al.* Capitation, managed care and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; **158**: 133–138.
13. Ruchlin HS, Dasbach EJ. An economic overview of chronic obstructive pulmonary disease. *Pharmacoeconomics* 2001; **19:** 623–642.
14. Hiller FC, Alderfer V, Goldman M. Long-term use of Viozan™ (sibenadet HCl) in patients with chronic obstructive pulmonary disease: results of a 1-year study. *Respir Med* 2003; **97** (Suppl A): S45–S52.
15. Ind PW, Laitinen L, Laursen L, *et al.* Early clinical investigation of Viozan™ (sibenadet HCl), a novel D_2 dopamine receptor, β_2-adrenoceptor agonist for the treatment of chronic obstructive pulmonary disease symptoms. *Respir Med* 2003; **97** (Suppl A): S9–S21.
16. Laursen LC, Lindqvist A, Hepburn T, *et al.* The role of the novel D_2/β_2-agonist, Viozan™ (sibenadet HCl), in the treatment of symptoms of chronic obstructive pulmonary disease: results of a large-scale clinical investigation. *Respir Med* 2003; **97** (Suppl A): S23–S33.